B. Election/Restriction

Applicants confirm that claims 33-62 have been withdrawn from this case in view of a restriction requirement.

C. Specification

The trademarks noted by the Examiner have been capitalized, pursuant to M.P.E.P. § 608.01(v).

D. Section 103 Rejections

All the pending claims have been rejected as obvious based on the three-way combination of (1) Vora, (2) Acharya, and (3) Benes. In view of the amendments and comments of this Response, Applicants respectfully traverse.

Three basic criteria must be met to establish a *prima facie* case of obviousness:

(1) there must be some suggestion or motivation, either in the References themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;

(2) there must be a reasonable expectation of success; and

(3) the prior art reference (or references when combined) must teach or suggest all the claim limitations.

M.P.E.P. § 2142.

Here, the Office has not established a *prima facie* case, for it has not established any of these three prongs.

1. The references, even when combined, do not teach or suggest all the claim limitations

Even if the three cited references were combined, all of the present claim limitations would not be taught or even suggested.

Amended independent claim 1 recites, in part, "A pharmaceutical gel composition comprising ... at least one pH-sensitive *film-forming polymer forming a film when applied to*

skin or a mucosal surface ... ." Independent claim 16 recites, in part, "A pharmaceutical *gel which when applied to the skin or mucosal surface forms a film*, said gel comprising ... at least one pH-sensitive film-forming polymer ... wherein said film is formed due to changes in pH and desolvation of the polymer ... ." (emphasis added). Such features are nowhere taught or suggested in the cited art, taken alone or in any combination.

Vora is directed to a method to treat aphthous ulcers using a paste, solution, gel, and other conventional formulations. [*See* col. 2, lines 42-47]. In contrast to the present invention, Vora nowhere discloses or suggests the use of a pharmaceutical gel utilizing a pH-sensitive film-forming polymer that, when applied to the skin or mucosal surface, forms a film.

Acharya is directed to the use of calcium polycarbophil gels to deliver active agents. [Abstract]. Acharya discloses the formation of a polymeric complex carrier formed by the interaction of calcium and polycarbophil. [Col. 3, lines 15-25]. Specifically, Acharya discloses that the composition is supplied as a two-part system, a polymer phase and a liquid phase. [Col. 3 lines 33-39]. Acharya nowhere discloses or suggests the use of a pharmaceutical gel utilizing a pH-sensitive film-forming polymer that, when applied to the skin or mucosal surface, forms a film.

Benes is directed to the use of a device for the delivery a heparinic anticoagulant across a mucosal surface. [Abstract]. The device includes a reservoir containing a matrix (*i.e.*, a gel, powder, or tablet containing a heparinic anticoagulant) and an outer mucoadhesive portion. [Figure 1]. The outer mucoadhesive portion is a *pre-formed* solvent-casted film combination of a polymeric resin (*i.e.*, Carbopol) with an elastomeric component. [Col. 5, lines 24-36]. Benes discloses the use of basic (cationic) polyamines such as EUDRAGIT E only to "neutralize" this resin. [Col. 6 lines 13-17]. As evidenced by Figure 1, this pre-formed outer mucoadhesive

coating is a pre-casted film (or "sheet") that is subsequently filled with a gel containing a heparinic anticoagulant (*see* Example 1). [*Also*, col. 9 lines 30-67].

Importantly, Benes nowhere teaches the use of a pharmaceutical *gel* including a pH-sensitive film-forming polymer that, *when applied to the skin or mucosal surface, forms a film.* Specifically, the disclosure of a gel residing within a reservoir defined by a pre-formed, neutralized film coating does not amount to the disclosure or even suggestion of a gel composition including a component that, upon application to the skin or mucosal surface, itself forms a film. In fact, it can be argued that the disclosure of Benes teaches away from such a concept because it effectively teaches the advantages of using a pre-formed film or sheet with a backing to create a gel-filled reservoir. [*See* Figure 1].

The Office's present arguments appear to be an improper piecing-together of disparate elements from different references. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 230 U.S.P.Q. 416 (Fed. Cir. 1986) ("It is impermissible within the framework of 35 U.S.C. § 103 to pick and choose from any on reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art."). For example, the Office argues that the film-forming component of the presently-recited gel is contained in Benes, when in fact, Benes simply mentions that Eudragit can be used to neutralize a resin within a pre-formed sheet. [Col. 6, lines 13-17; *also* Figure 1]. The mere naming of Eudragit in the Benes reference (in a different context) does not establish the claimed elements, nor does it advance any basis for obviousness under an "inherency" theory. *In re Newell*, 13 U.S.P.Q.2d 1248 (Fed. Cir. 1989) ("[A] retrospective view of inherency is not a substitute for some teaching or suggestion *which supports the selection and use of the various elements in the particular claimed combination.*") (emphasis added).

Accordingly, none of the cited teaches or even suggests the elements required by all the pending claims — particularly the pH-sensitive film-forming polymer that forms a film when applied to skin or a mucosal surface. Thus, there can be no *prima facie* case of obviousness, and the pending claims are accordingly in condition for allowance.

2. There is no suggestion or motivation to modify the references or to combine the reference teachings

In order for the cited references to even arguably be pertinent, one of ordinary skill in the art would have to significantly modify Benes, which discloses that EUDRAGIT is used simply to neutralize a pre-formed outer film layer that encases a reservoir of gel. [Col. 6 , lines 13-17; *also*, Figure 1]. In particular, Benes would have to modified so that the EUDRAGIT, instead of simply neutralizing the pre-formed outer coating, would instead be appropriately combined in a particular gel composition in such a way that a film would form upon application to the skin or mucosal surface. [*See, e.g.*, independent claims 1, 16]. No such motivation exists (or is cited by the Office) for this modification. Further, such a modification would change the operation of Benes — instead of utilizing a pre-formed film encasing a reservoir, Benes would operate by utilizing a gel that itself formed a film upon application. Accordingly, this modification is improper. *See* M.P.E.P. 2143.01 ("If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious."). The claims are therefore in condition for allowance.

3. The Office has not established that there would be a reasonable expectation of success

The Office has not shown or argued the required reasonable expectation of success. Applicants respectively submit that there is nothing in the cited art that demonstrates a reasonable expectation of success surrounding the significant modification of Benes discussed above. In particular, there is nothing in the record to suggest that the abandonment of the pre-formed film encasing a gel in Benes in favor of a different gel composition including a film-forming polymer that forms a suitable film upon application to the skin or mucosal surface would be successful. Accordingly, for this reason as well, the claims are not *prima facie* obvious and should be allowed to issue.

III. PETITION FOR EXTENSION OF TIME

Pursuant to 37 C.F.R. § 1.136(a), Applicants petition for an extension of time of one month up to and including September 8, 2002 in which to respond to the Office Action dated May 8, 2002. Pursuant to 37 C.F.R. § 1.17, the extension fee is $55.00. A check is enclosed. Should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the enclosed materials, or should an over and under-payment be included herein, the Commissioner is authorized to deduct or credit fees from or to Fulbright & Jaworski Deposit Account No. 50-1212/10111431/MCB.

CONCLUSION

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants respectfully request that the rejections of all claims be withdrawn so the claims may swiftly pass to issuance.

Should the Examiner desire to sustain any of the rejections discussed in relation to this Response, the courtesy of a telephonic conference between the Examiner, the Examiner's supervisor, and the undersigned attorney at 512-536-3018 is respectfully requested in advance.

Respectfully submitted,

Michael C. Barrett

Michael C. Barrett
Reg. No. 44,523
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
Telephone: (512) 474-5201
Facsimile: (512) 536-4598

Date: August 20, 2002

APPENDIX A -- AMENDMENTS

In the Claims:

1. (Amended) A pharmaceutical gel composition comprising:

a solvent vehicle,

at least one water-insoluble swellable mucoadhesive polymer,

at least one pH-sensitive film-forming polymer forming a film when applied to skin or a mucosal surface, and

at least one molecule of interest.

4. (Amended) The gel of claim 1, wherein the water-insoluble swellable mucoadhesive polymer is [Noveon] NOVEON or [Carbomer] CARBOMER.

8. (Amended) The gel of claim 1, wherein the pH-sensitive polymer is a [Eudragit] EUDRAGIT polymer, or a chemical derivative thereof.

19. (Amended) The gel of claim 16, wherein the water-insoluble swellable mucoadhesive polymer is [Noveon] NOVEON or [Carbomer] CARBOMER.

23. (Amended) The gel of claim 16, wherein the pH-sensitive polymer is a [Eudragit] EUDRAGIT polymer, or chemical derivative thereof.

In the Specification:

Page 5, second-to-last paragraph:

The solvent vehicle may be comprised of at least 25 to 100 parts water or buffered water with 0 to 75 parts of ethanol, propylene glycol, glycerin, polyethylene glycol, or combinations thereof. The water-insoluble swellable mucoadhesive polymer may be polyacrylic acid cross-linked with polyalkenyl ether or divinyl glycol, wherein the water-insoluble swellable mucoadhesive polymer is preferably, [Noveon] NOVEON or [Carbomer] CARBOMER. The water-insoluble swellable mucoadhesive polymer may be present at a concentration of from 0.1% to 20% by weight.

Page 6, second paragraph:

The invention is also directed to a pharmaceutical gel which when applied to the skin or mucosal surface forms a film, said gel comprising a solvent vehicle, at least one water-insoluble swellable mucoadhesive polymer, at least one pH-sensitive film-forming polymer, and at least one molecule of interest, wherein said film is formed due to changes in pH and desolvation of the polymer, and wherein said film provides for the delivery of the molecule of interest to or through the application site. The solvent vehicle may be comprised of at least 25 to 100 parts water with 0 to 75 parts of ethanol, propylene glycol, glycerin, polyethylene glycol, or combinations thereof. The water-insoluble swellable mucoadhesive polymer may be polyacrylic acid cross-linked with polyalkenyl ether or divinyl glycol. Preferably, the water-insoluble swellable mucoadhesive polymer is [Noveon] NOVEON or [Carbomer] CARBOMER. The water-insoluble swellable mucoadhesive polymer may be present at a concentration of from 0.1% to 20% by weight.

Page 7, second paragraph:

The water-insoluble swellable mucoadhesive polymer is polyacrylic acid cross-linked with polyalkenyl ether or divinyl glycol. Preferably, the water-insoluble swellable mucoadhesive polymer is [Noveon] NOVEON or [Carbomer] CARBOMER. The water-insoluble swellable mucoadhesive polymer may be present in the pH-sensitive mucoadhesive layer at a concentration of from 0.1% to 20% by weight.

Page 9, second-to-last paragraph:

Figure 2 shows an *in vitro* adhesion time of ¼ inch wax-film composites (n=3 each) on glass submerged in 40 mM KH_2PO_4/NaOH buffer, pH 6 at 37°C (unstirred). Each mucoadhesive layer contains 5.0-5.3 mg of total polymer comprised of [Noveon] NOVEON and [Eudragit] EUDRAGIT S100 in the ratios indicated. The wax layer consists of DENTSPLY® Utility Wax containing 1% w/w tragacanth polymer. *Indicates that different volumes of mucoadhesive gels were cast as described in Example 8. See Table 1 and Example 8 for additional details.

Page 9, last paragraph:

Figure 3 shows *in vitro* adhesion time of ¼ inch wax-film composites (n=3 each) on glass submerged in 40 mM KH_2PO_4/NaOH buffer, pH 6 at 37°C (stirred at 100 rpms). Each

mucoadhesive layer contains from 1.2 mg to 11.2 mg of total polymer comprised of [Noveon] NOVEON and [Eudragit] EUDRAGIT S100 in a weight ratio of 3:1. The wax layer consists of DENTSPLY® Utility Wax containing 1% w/w tragacanth polymer. See Table 2 and Example 9 for additional details.

Page 10, third full paragraph:

Figure 6 shows the release of plasmid DNA pre-loaded into wax-film composites. Wax-film composites were made as described in Example 10 using a mucoadhesive gel comprised of [Noveon/Eudragit] NOVEON/EUDRAGIT S100 (3:1 w/w) and plasmid DNA. The wax layer consists of DENTSPLY® Utility Wax containing 1% w/w tragacanth polymer. Five ¼ inch wax-film composites containing of plasmid DNA (5 μg) were submerged separately into 1 mL 10 mM PBS buffer, pH 7.4 at 37°C. At various times, exactly 100 μL solution was aliquoted for DNA quantitation using the PicoGreen DNA Quantitation Kit. Exactly 100 μL fresh PBS was added to replace the removed volume at each time point.

Page 10, fourth full paragraph:

Figure 7 shows the release of plasmid DNA post-loaded into wax-film composites. Wax-film composites were made as described in Example 10 using a mucoadhesive gel comprised of [Noveon/Eudragit] NOVEON/EUDRAGIT S100 (3:1 w/w). The wax layer consists of DENTSPLY® Utility Wax containing 1% w/w tragacanth polymer. Plasmid DNA (5 μg) was added to five individual ¼ inch wax-film composites, allowed to air dry for 4 hours, and then submerged separately into 1 mL 10 mM PBS buffer, pH 7.4 at 37°C. At various times, exactly 100 μL solution was aliquoted for DNA quantitation using the PicoGreen DNA Quantitation Kit. Exactly 100 μL fresh PBS was added to replace the removed volume at each time point.

Page 25, first full paragraph:

A plethora of different mucoadhesive gel formulations have been described in the literature and several are now marketed products. Typically, the mucoadhesive component of the formulation is a biocompatible polymer, such as polyacrylic acid that is cross-linked with an acceptable agent to create an insoluble gel. The use of an insoluble gel is desirable since it remains in contact with the mucosal tissue for much longer periods of time. Cross-linked

polyacrylic acid polymers, such as [Noveon] NOVEON and [Carbomer] CARBOMER, have been shown to stay attached to the mucosal lining in the vagina for up to three to five days (March and Nakamura, 1993). Further, gels containing [Noveon] NOVEON and/or [Carbomer] CARBOMER have been used as vaginal lubricants so it is envisioned that the described gels may be used during sexual intercourse. [Noveon] NOVEON and [Carbomer] CARBOMER-based polymers are weak acids and contain many negatively-charged carboxyl-groups. The multiple negative charges on these polymers promote hydrogen-bonding between the polymers and the negatively charged mucin, the main glycoprotein that allows for the attachment of mucus to the epithelial lining of the vaginal wall (Park and Robinson, 1985). [Noveon] NOVEON and [Carbomer] CARBOMER-based polymers have been shown to have maximum hydrogen-bonding in the pH range of 4.0 to 6.0. This is ideal for use in the vagina which has a normal pH value of about 4.5 (Stevens-Simon et al., 1994; Garcia-Closas, et al., 1999). It is envisioned that gels comprised of pH-sensitive polymers and water-insoluble mucoadhesive polymers such as [Noveon] NOVEON and [Carbomer] CARBOMER may provide superior delivery of molecules of interest to the vagina since the lower pH of the vagina will cause the pH-sensitive polymer to form a long lasting film to retain and/or deliver the molecule of interest in a more efficacious manner.

Page 26, first paragraph:

Materials: Recombinant hirudin and bovine α-thrombin are from Sigma Chemicals (St. Louis, MO). Chromozym-TH is from Boehringer Mannheim. Chitosan Seacure 143 (85-90% deacetylated) is from Natural Biopolymer Inc. (Raymond, WA). All [Eudragit] EUDRAGIT polymers were obtained from Rohm America, Inc. (Piscataway, NJ). [Noveon] NOVEON and [Carbomers] CARBOMERs were obtained from BF Goodrich (Cleveland, Ohio). Glycerin, polyethylene glycol 400, isopropyl myristate, ethanol, sodium hydroxide, and propylene glycol were all of USP/NF grade and were purchased from Spectrum Quality Products, Inc. (New Brunswick, NJ). PicoGreen dsDNA Quantitation Kit was purchased from Molecular Probes, Inc. (Eugene, OR). DENTSPLY® Utility Wax was obtained from DENTSPLY International (York, PA).

Page 26, second paragraph:

A placebo pH-sensitive mucoadhesive film-forming gel was made as follows. Water (44.1 % w/w) was added to a 250 mL stainless steel beaker and stirring was begun at 200 rpm using a Caframo Stirrer. [Noveon] NOVEON (0.5% w/w) and [Carbomer] CARBOMER 971 (0.8% w/w) were added very slowly to the stirring water until the solution was clear and viscous with no visible solid material in solution. Glycerin (50.4% w/w) was then added to the polymers in water. [Eudragit] EUDRAGIT L100 (2.0% w/w) was added and the solution and the viscous solution became slightly milky in color and less viscous. 18% sodium hydroxide (2.2% w/w) was then added and the whitish gel became viscous. The pH of the placebo gel was measured by taking 1 mL of the gel and dispersing it into 5 mL water and measuring the pH after 1 hour. The pH of the gel was 6.3 ± 0.02 ($n = 3$). When the placebo gel was spread onto the skin of a human volunteer's hand; it produced a clear film. Placebo gel stored under controlled conditions at 25°C/60% Relative Humidity for 1 week and 1 month had pH of 6.2 ± 0.07 ($n = 3$) and 6.2 ± 0.06 ($n = 3$), respectively. Placebo gel stored under controlled conditions at 40°C/75% Relative Humidity for 1 week and 1 month had pH of 6.1 ± 0.03 ($n = 3$) and 6.1 ± 0.09 ($n = 3$), respectively. These results demonstrated that the placebo gel was stable when stored under the conditions tested.